

committee immediately and report at once as to its personnel to the Secretary of the State Society, in the enclosed envelope.

Yours truly,

RENÉ BINE,

Chairman Committee on Health Insurance.
Address: 350 Post Street, San Francisco.

ANOTHER SWINDLER.

A rather clever way of getting a few dollars out of the doctor came to our attention last month, and is worthy of record for reference. A workman appeared in the office of a specialist in San Francisco, with a letter purporting to come from Gordon and Gillis, General Contractors, asking the doctor to take professional care of one of their valued employees, a Mr. Leroy Williams. The patient was carefully examined and was advised that his case would require a somewhat long period of treatment. He asked about what the expense would be and was told; whereupon he stated that he would like to pay something on account, and produced what appeared to be a draft for \$85.00, asking the physician to take out \$25.00 and give him the rest. This particular doctor, being cautious, told him he would send the check to the bank and the man could come the next day and get his money. It is needless to say that the check was returned by the bank, unpaid, and that the man never showed up again.

NEW VIEWS ON TUBERCULOSIS.

Dr. Maurice Fishberg, a review of whose book on pulmonary tuberculosis will be found elsewhere in the JOURNAL, has presented in a very striking and original way a number of thoughts in regard to tuberculosis that are well worth our careful consideration. The review of his book, already referred to, is extensive, and will give any one interested an excellent idea of its range and scope.

— NOTICE —

The California State
Journal of Medicine and
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— DOUGLAS 62 —

ORIGINAL ARTICLES

SECOND THOUGHTS ABOUT SALVAR-SAN THERAPY.*

By WILLIAM E. STEVENS, M. D., San Francisco.

As the supply of salvarsan and neosalvarsan has been temporarily discontinued it seems appropriate at this time to consider some of the contraindications for their use and common errors in the technic of the various methods of administration. These preparations, of great value in the treatment of syphilis, contain large amounts of arsenic and are capable of producing some very disastrous and even fatal results when incorrectly employed. This important fact seems to have been lost sight of, for salvarsan has been carelessly, even recklessly, used by many reputable practitioners.

CHOICE OF PREPARATIONS.

Neosalvarsan should be discarded in favor of salvarsan except in those few instances where there are grounds for the belief that an idiosyncrasy exists, or when administration in the office is imperative. The superiority of the latter over the former drug is shown by Nelson and Haines of the Fort Leavenworth, Kansas, Military Prison, who report twice as many negative Wassermann reactions after four injections of salvarsan with mercurial treatment as were obtained after five injections of neosalvarsan and the same amount of mercury. E. H. Martin of Hot Springs, Ark., obtained similar results.

CONTRA-INDICATIONS.

Only positive indications should warrant the employment of this drug. The following cases reported by Brandenburg and Kannengiesser illustrate this fact. A robust man had undergone thorough anti-syphilitic treatment four years previously and although his blood was negative to repeated Wassermann tests, and his wife and children were likewise healthy, he was nevertheless given an intravenous injection of 0.5 grams of salvarsan; vomiting and diarrhea followed immediately and the patient died in convulsions four days later. Kannengiesser's patient was a robust man of 29 who developed convulsions followed by death three hours after salvarsan. No cause was found on autopsy.

Another patient suffered from an anemia for which no cause could be found. Salvarsan was given intravenously in doses of 0.1 and 0.2 grams on consecutive days. Seventy-two hours later paralysis of both arms developed. Recovery followed, but the arms were still weak six months after the treatment.

Davidson of Los Angeles reports the case of a vigorous young man suffering from secondary lues who immediately after the injection of 0.6 of neo-salvarsan became cyanosed, pulseless and suffered agonizing pain in the precordium. He recovered some hours later, however, following frequent injections of adrenalin solution and saline enemas. Davidson thought the collapse probably due to the vaso dilation caused by the salvarsan superimposed

* Read before the San Francisco County Medical Society, November 30, 1915.

upon a similar action of alcohol some of which was detected in the patient's vomitus.

The eight deaths in Los Angeles following the intraspinal administration of salvarsan are still fresh in our memory.

These serious results, together with a large number of others reported in the literature, should be sufficient warning against the indiscriminate use of this powerful drug.

In the majority of cases fatalities occur after the second or subsequent doses, the usual symptoms being either those of meningeal involvement, uremia resulting from nephritis, toxemia following degenerative processes in the liver, or pulmonary embolism due to phlebitis and thrombosis at the site of the injection into the vein. This last complication is obviously more likely to result from 606 than from the less irritating 914.

Sachs, Strause and Kaliski give the following list of contraindications for the use of salvarsan: Severe renal involvement; marked cardiac disease with insufficiency of the cardiac muscles; impending coma in diabetes or nephritis; terminal conditions not likely to be benefited by salvarsan and a known intolerance to the drug. To this list may be added, severe gastro-intestinal or hepatic diseases and advanced cancer.

Likewise during pregnancy if there is any doubt as to the condition of the kidneys, functional tests should be made to decide the question. Phenol-sulphonaphthalein or phloridzin as tests of excretion and blood cryoscopy or blood urea as tests of retention, are of most value.

Salvarsan should be used with great caution when there is involvement of nerve tissue, especially if severe headache exists or symptoms of upper cervical cord or medulla involvement are present. Also in cases of chronic poisoning from alcohol, nicotine, or lead, in tuberculosis or other infectious diseases, in Addison's disease, status lymphaticus and in fact whenever the vitality is lowered from any cause.

IMPROPER PREPARATION OF THE SOLUTION.

Four cases may be mentioned in which the sodium hydrate was unintentionally omitted in making up the salvarsan solution. The first occurred in my own practice, the patient being a woman 38 years old who had been infected by her husband twelve years previously. When the secondary symptoms appeared she was informed that she was suffering from Cuban itch, and no specific treatment was given. Three months before coming under my care she began to experience a slight numbness of the legs with some difficulty in walking. Examination revealed an absence of the patellar reflexes with a slight loss of tactile sensation on the outer surfaces of both legs. Her blood Wassermann was three plus positive. The spinal fluid Wassermann, globulin and cell count were negative and except for a diminished amount of hemoglobin (sixty per cent.) and a reduction in the number of red blood cells (3,900,000), she was otherwise healthy. She was given intravenously 0.4 grams of salvarsan in 100 cc. of warm sterile distilled water from which the sodium hy-

drate solution was omitted. A slight erythema developed and five minutes later upon attempting to rise from the table she lost consciousness; she recovered almost immediately, however, but was very weak for three days.

The second case occurred in the practice of a colleague. The patient was a married woman 17 years of age, in whom a diagnosis of lues had been made although no Wassermann examination had been obtained. She was given intravenously 0.6 grams of salvarsan in 200 cc. of cold non-alkaline solution. Almost immediately she became unconscious and remained so for about twelve hours. Her temperature rose to 104°, sugar appeared in the urine, also a trace of albumen; her ankles became swollen, and for several days she complained of intense pain in the head and back, but eventually recovered.

A third case, seen in consultation by a colleague, developed a profuse erythema following the injection. This cleared up, however, in about five minutes. Further history of the case was not obtained.

The only report of a similar accident that I have been able to discover in the literature is that of Eberly of Fort Wayne, Ind. His patient received 5 cc. of an unneutralized solution containing 0.6 grams of salvarsan in 10 cc. of water. Pronounced symptoms of collapse appeared almost instantly, but were relieved by frequently repeated doses of nitroglycerine. A complete suppression of urine lasted three days. A severe phlebitis began in the cephalic vein and lasted six weeks. The urine was not free from albumen nor had the patient recovered her strength until the same period of time had elapsed.

Another common error in technic is the neglect to filter the solution before use. It is easy to understand how particles of glass from the ampoule or small portions of undissolved salvarsan might be injected into the vein with the unfiltered preparation. That freshly distilled sterile water should always be used is almost needless to mention. It is now recognized that many of the unpleasant results heretofore reported following the use of this drug were due to the water in which it was dissolved.

IMPROPER METHOD OF ADMINISTRATION.

Strange as it may seem, some physicians continue to cut down upon the vein before inserting the needle. In one case recently called to my attention a young dental student received four salvarsan injections, and with them a like number of scars on his arms to carry through life as mementoes of the occasion. This is absolutely unjustifiable, for even in a small child a vein of sufficient size can be felt if not seen. When the median basilic is deeply situated or small, often the cephalic, median cephalic, radial or ulnar, veins will be found satisfactory. In infants a vein of the scalp, the external jugular or injection into the superior longitudinal sinus through the anterior fontanelle is preferable.

The precaution should be taken to make certain that the needle is in the vein during the injection of the salvarsan. If a Luer syringe barrel be at-

tached to the rubber tubing a regurgitation of blood into the barrel is evidence that the needle is in the vein and that the injection may be proceeded with. Much suffering and deformity has followed the escape of this irritating solution into the surrounding tissues. I have in mind a young girl to whom this accident occurred two years ago. An enormous scar resulted and although her Wassermann reaction is now three plus positive she could never be persuaded by the attending physician to take another injection. Intramuscular injections have been justly discarded by almost everyone.

Authorities differ widely regarding the proper dosage and the intervals at which salvarsan should be administered. Small doses at frequent intervals are not advisable, a resistance to these being acquired by the spirochetes, many of which escape destruction whereas they are overwhelmed and greater numbers destroyed by larger amounts. It should be remembered, however, that in the secondary stages of syphilis the initial dose of salvarsan should not be too large for at this time the danger of brain disturbances and Herxheimer reactions is greatest.

INTRADURAL MEDICATION.

Although much has been written and many cases reported in which patients have been subjected to intradural medication no consensus of opinion exists as to the permanent value of this method of therapy.

Many advance the argument that the blood supplies all living tissue with nourishment and any substance dissolved in it will be carried to the brain, the cord, and every other part of the body in which the blood circulates. In this connection, attention is called to the fact that in arsenical poisoning degeneration of the anterior horn cells of the cord occurs.

Nonne was unable to observe any difference in the course of cases treated with salvarsanized serum from that of others treated with the older methods. Personally I have not seen any brilliant results, although it cannot be denied that many cases have shown temporary improvement at least. In the Swift-Ellis method this is without doubt achieved in many instances with the help of the intravenous injection which precedes the intraspinal administration of the salvarsanized serum. In many cases the rest and attention which of necessity accompany the treatment are partly responsible for the improvement noted, and finally it must be remembered that remissions are characteristic of syphilis of the central nervous system. It seems reasonable to believe, however, that the arsenic and the antibodies introduced into the spinal canal, as well as the removal of a quantity of abnormal spinal fluid, would prove of benefit. In fact, the withdrawal of the same amount of spinal fluid alone will produce favorable alteration in the serobiologic findings. It should be borne in mind that Wechselmanns, Sicard and Block, Zoloziechi, Kapland and others detected arsenic in the spinal fluid after the third or fourth injections of salvarsan or neosalvarsan given by the intensive method. Professor Benedict of Cornell found more arsenic in the spinal fluid twenty-four hours after the intrave-

nous administration of salvarsan than was present in a like amount of salvarsanized serum.

In this connection the suggestion of decreasing the pressure of the spinal fluid after the intravenous injection of salvarsan made by George Hall and carried out by J. H. Barbat in a case reported recently is of interest. In Barbat's case 43 cc. of cerebrospinal fluid were withdrawn immediately after the intravenous injection of 0.9 of neosalvarsan. This was done with the idea that the lost spinal fluid would be replaced at a time when the blood contained the maximum amount of the drug. A specimen of spinal fluid removed four days later showed 1 to 100,000 metallic arsenic. It is impossible to obtain a larger amount after the introduction of salvarsanized serum according to the Swift-Ellis technic. Neosalvarsan was used because of the fact that this preparation is thought to remain in the blood serum rather than enter and remain in the red cells as does the older drug.

It might be added, however, that in the majority of cases reported in the literature in which arsenic was found in the spinal fluid intravenous injections of salvarsan had preceded the examination. None was found when neosalvarsan had been used.

I have recently used this method in two tertiary cases, one with positive, and the other with negative blood and spinal fluid findings. In the first case 0.9 of neosalvarsan were administered intravenously and 30 cc. of spinal fluid immediately withdrawn. Examination ten days later showed no trace of arsenic. At this time 0.6 of salvarsan were injected intravenously and 30 cc. of spinal fluid withdrawn. Notwithstanding the fact that the spinal fluid withdrawn the following day was contaminated by a small amount of blood it contained no arsenic.

In my other case 0.6 of salvarsan were injected intravenously; 35 cc. of spinal fluid were immediately withdrawn. Half of this escaped in a stream under considerable pressure. Examination of the spinal fluid 48 hours later showed a trace of arsenic.

Whenever the Swift-Ellis method of intradural injection of salvarsanized serum is justifiable, the intensive combined treatment having been tried and failed, the technic of the originators of the method should be strictly adhered to. It seems to be a common practice to use a serum prepared from blood which shows a positive Wassermann reaction when the spinal fluid is negative to all serobacteriological tests. In my opinion this procedure is altogether unwarranted, and no benefit can result therefrom.

Freyermuth in a recently reported series found that in every case where the spinal fluid became negative the blood Wassermann was negative prior to the treatment with salvarsanized serum.

Another not infrequent error is in the injection of a larger amount of serum than the quantity of spinal fluid withdrawn. An illustration of this may be mentioned which occurred in the practice of a local physician. Eleven centimeters of spinal fluid were removed and 27 centimeters of serum injected. The patient immediately complained of excruciating pain over the entire body which was

only relieved after the withdrawal of 35 cc. of spinal fluid. He was confined to his bed for four days, but finally recovered. In another case worthy of mention the unfortunate patient died two hours after this mistake had been made, the autopsy showing cerebral hemorrhage. Another fatality resulted shortly after the injection of a large quantity of air into the spinal canal, and a third patient died ten hours after the injection of 20 cc. of a salvarsanized serum which had not been inactivated. The value of these observations, however, is lessened by the fact that the complete histories of the cases could not be obtained.

The following brief history was called to my attention by a colleague who had attended the patient. It illustrates the result of faulty antisepsis.

Mrs. A. contracted syphilis in 1901 and received treatment for two years following the appearance of the secondaries. In October, 1913, symptoms of tabes appeared; the blood Wassermann was three plus positive. She was given eight intravenous injections of salvarsan at intervals of one month. These were followed by mixed treatment for four months. Examination of the blood on October 12, 1914, showed a two plus Wassermann reaction. Three more intravenous injections of salvarsan and one injection of neosalvarsan were given at intervals of two weeks. On January 30, 1915, the blood Wassermann was negative, but the spinal fluid showed a three plus positive and a cell count of 34. Thirty cc. of salvarsanized serum were injected intraspinally on February 12, 1915. The headache disappeared and the spinal symptoms improved. On April 6th another intradural injection of 32 cc. was given, marked improvement resulting. All symptoms disappeared, the patient stating that she had never felt better in her life. On May 2nd examination of the spinal fluid showed a one plus Wassermann. On May 8th a third intraspinal injection consisting of 25 cc. of serum was given. The next evening the patient complained of severe headache and pain in the back of the neck. The temperature was 102°. The following day the temperature reached 104°, the next day 106° with delirium. The spinal fluid was very cloudy and contained many pus cells and gram positive bacilli. The Wassermann was negative. Death supervened on May 13th.

The infection was probably caused by the hands of the nurse who had handled the plunger and barrel of the syringe after removing them from the sterilizer.

In the two following cases neosalvarsan was injected directly into the spinal canal. Gordon's patient was a tabetic of 35, whose most prominent symptoms were pain in the lower extremities, ataxia, incontinence of urine and constipation. He had at one time been treated with potassium iodide and mercury. The Wassermann was positive in blood and spinal fluid. After one injection of salvarsanized serum all symptoms improved with the exception of the constipation. Two months later the bladder disturbance returned and this time neosalvarsan dissolved in the spinal fluid was injected directly into the canal according to the

technic of Ravaunt. This was followed by severe pain in the legs and vomiting. Retention of urine and incontinence of feces began. Erythematous patches, later becoming gangrenous, appeared on the penis, scrotum and sacrum. Two weeks later he was unable to walk; sleep was impossible on account of the agonizing pain in the legs. All symptoms became gradually worse until death supervened.

In the other case mentioned in a recent journal of a patient with general paresis, three weeks after the sixth intraspinal injection of neosalvarsan, all of the injections having been tolerated without great discomfort, an acute ascending paralysis of the Landry type developed and death supervened.

In view of such disasters I do not consider advisable the intradural injection of salvarsan or neosalvarsan dissolved either in water or spinal fluid or the addition of these preparations to salvarsanized serum.

CONCLUSION.

My conclusion may be expressed in the form of "Don'ts":

Don't use salvarsan unless positive indications for its employment exist.

Don't expect as much from neosalvarsan as from salvarsan.

Don't give salvarsan in the office.

Don't give salvarsan at too frequent intervals or in too small doses.

Don't omit any details in preparing the solution to be injected.

Don't neglect to filter the solution before it is injected.

Don't cut down on a vein.

Don't inject any of the solution into the tissues surrounding the vein.

Don't administer too large a dose at the first injection, especially in the early secondary stages.

Don't inject salvarsanized serum prepared from a Wassermann positive blood into a canal containing Wassermann negative spinal fluid.

Don't inject a quantity of salvarsanized serum larger than the amount of spinal fluid removed.

Don't inject air into the spinal canal.

Don't use intradural medication under any circumstances until the intensive treatment with intravenous injections of salvarsan, mercury inunctions or injections and potassium iodide has been given a thorough trial.

Discussion.

Dr. M. Krotoszyner: Dr. Stevens' paper contains a wealth of important information on salvarsan therapy, and, therefore, must be considered a valuable contribution to our knowledge of the use and abuse of that important drug. While I agree, theoretically, with Dr. Stevens' objection to the application of the old salvarsan in office practice, I, nevertheless, have been compelled to use it of late, owing to the want of neosalvarsan. Fortunately I have, so far, seen no untoward result, in spite of repeated ambulatory administration of the drug.

Dr. Stevens' objection to neosalvarsan is, in my opinion, too sweeping. It is a very valuable remedy and, in the great majority of cases, perfectly sufficient in its efficacy, while its administration is not fraught with the dangers so often encountered in connection with the old salvarsan.